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# Novel flavonoids as anticancer agents: mechanisms of action and promise for their potential application in breast cancer

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## Introduction

Flavonoids account for the largest group of secondary metabolites in the plant kingdom. They comprise over 5000 ubiquitous compounds with a common polyphenolic backbone (see *Table 1*) and have essential roles in plants[1].

Among other health-promoting properties, numerous studies have reported interesting preclinical activity in cancer models for a wide range of cancers, suggesting their potential use in treatment and prevention of cancer. This has been the basis for numerous studies and trials in different models and types, including extensive research on breast tumours[2–4].

Research has reported the involvement of numerous mechanisms in the effect of flavonoids against cancer. These are not mutually exclusive, but evidence supports the potential of these compounds to target different pathways and mechanisms underlying the complexity of cancer as a disease. Due to limitations on space, this review will not focus on the numerous clinical trials and studies evidencing the effect of flavonoids on cancer. Instead, it will focus on the most relevant of their different properties and summarise their complex potential mechanism of action in breast cancer in particular.

## Flavonoids as antioxidants

The role of flavonoids as antioxidants has been the subject of research for decades[5,6]. The numerous hydroxyl groups in the flavonoid structure, in combination with a highly conjugated,  $\pi$ -electron system, allow them to act as free radical scavengers by hydrogen atom or electron donating activities. Furthermore, they can block formation of reactive oxygen species (ROS), such as the hydroxyl radical, through chelation of redox-active, transition metal ions[6]. This can have a positive effect on cancer prevention by minimisation of phenomena such as oxidative damage to DNA.

Research on breast cancer cell lines has shown that polyphenols exert strong inhibitory effects due to their antioxidant properties antagonising the oxidising activity of  $H_2O_2$  by

scavenging ROS, or inhibiting ROS production[7]. Interestingly, there is also evidence that they can act as pro-oxidative compounds. For instance, myricetin can undergo auto-oxidation and reduce molecular oxygen to the superoxide free radical[8]. This dual effect suggests that a balance of both anti- and pro-oxidative properties might be essential to the role of flavonoids in the prevention or treatment of disease.

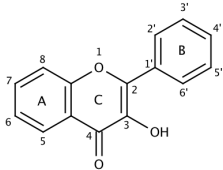
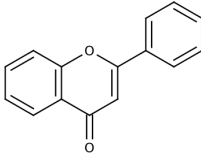
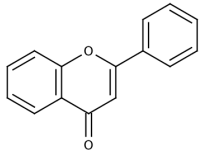
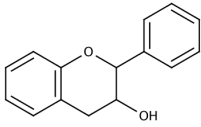
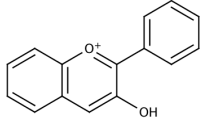
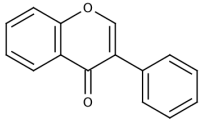
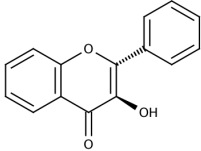
### *Flavonoids as phytoestrogens*

Some subtypes of flavonoids have often been referred to as phytoestrogens due to their ability to mimic oestrogen-like responses. They resemble the most important type of oestrogen in humans, 17 $\beta$ -oestradiol (E<sub>2</sub>), due to the existence of hydroxyl groups and phenolic rings (required for binding oestrogen receptors  $\alpha$  and  $\beta$  (ER $\alpha$  and ER $\beta$ ))[9].

Flavonoids can bind both isoforms of ER, mainly as agonists competing with E<sub>2</sub>[7], inducing biological responses traditionally associated with the binding of the natural hormone in a dose-dependent manner[10,11]. Studies have reported that some of the ER-mediated responses induced by flavonoids are nonetheless comparable, or even higher, to those induced by physiological levels of E<sub>2</sub>, one reason why some flavonoids are still described as full oestrogen agonists[12].

Unlike E<sub>2</sub>, several studies have reported a stronger affinity of flavonoids for the ER $\beta$  isoform[13] and also that flavonoids binding ER $\beta$  induce the transcription of oestrogen target genes to much greater levels than when binding ER $\alpha$ [14]. Critically, ER $\beta$  is known to exert a response opposing the proliferative effects of ER $\alpha$  activation[15]. Indeed, interaction between both types of receptors and their substrates provides a regulation for the overall effect of oestrogens and the ratio of ER $\alpha$ /ER $\beta$  is used as a prognostic marker in breast tumours[16]. This means that physiological levels of phytoestrogens are likely to activate ER $\beta$  but not the ER $\alpha$ -mediated pro-cancer signalling (or activate this to a much lower extent), therefore facilitating a beneficial antiproliferative effect.

Phytoestrogens can also alter the level of oestrogen biosynthesis, acting as aromatase inhibitors (AI) on cytochrome P450 19 aromatase (Cyp19), 17 $\beta$ -hydroxysteroid dehydrogenases (HSD) and oestrone sulfatase and sulfotransferase[17], all involved in the generation of oestradiol in breast tissue and associated with breast cancer when overexpressed. Some flavonoids have been shown to induce a significant decrease in circulating oestrogen concentration. Although their efficacy is lower than that of clinically used steroidal aromatase inhibitors, they could be very beneficial to treat tumours which exhibit a lack of response to common therapies. Additionally, flavonoids can also alter oestrogen-metabolising enzymes, thus reducing the production of genotoxic metabolites. Some *in vivo* studies have been carried out on animal models, although the complexity of these modulations needs to be further elucidated[18].

Subclass	Structure	Examples	Dietary sources	E.D.I. (mg)
Flavonols		Quercetin, kaempferol, myricetin and their glycosides	Onions, red wine, tea, fruits, berries and herbs	12.9
Flavones		Luteolin, apigenin and tangeretin	Herbs, celery and chamomile tea	1.6
Flavanones		Naringenin, hesperetin (found in diet mainly as glycosides)	Citrus fruits	14.4
Flavanols		Catechin, epicatechin, epigallocatechin	Cocoa or dark chocolate, apples, grape, red wine and green tea	156.9
Anthocyanidins		Cyanidin, delphinidin, pelargonidin, malvidin	Berries and other fruits	3.1
Isoflavones		Genistein, daidzein, glycitein and their glycosides	Soy products	1.2
Flavanonol		Taxifolin, aromadetrin	N/A	N/A

**Table 1** Flavonoids are polyphenolic derivatives consisting of a 3-ring basic backbone: 2 fused ring (aromatic A ring and heterocyclic C ring), connected to another aromatic B ring through a carbon-carbon bridge. According to changes in this molecular backbone and the presence of hydroxyl groups and other moieties, they can then be categorised into a further 7 subclasses[1], most of which are found in numerous dietary sources. This table includes examples compounds for each flavonoid subclass, dietary sources and estimated daily intakes (E.D.I.)[19]. Flavanonols have not been reported at significant levels in dietary sources.

### *Flavonoids as CYP1A1 inhibitors/substrates*

The impact of diet and environment in the development and progression of cancer is partially due to the exposure to polycyclic aromatic hydrocarbons (PAHs) and other xenobiotic carcinogenic compounds. PAHs such as benzo( $\alpha$ )pyrene (BaP), found in tobacco smoke or charred foods, can give rise to cancer after being subject to oxidation by cytochrome P450 (CYP1), a family of extrahepatic enzymes with monooxygenase activity.

The CYP1 family has been implicated in carcinogenesis and cancer progression through three main mechanisms: firstly, the CYP1 family modifies and activates PAHs and other pro-carcinogens, allowing them to bind DNA and give rise to cellular and genetic damage, essential in the cancer initiation stage[20]; secondly, the CYP1B1 isoform is involved in the modification of steroidal hormones such as oestradiol, contributing to the initiation of mammary carcinogenesis[21]; finally, the same isoform has also been shown to hinder cancer treatment by inactivation of a range of clinically used anticancer drugs[22].

Following the role of CYP1 in the development of cancer, extensive research has been carried out to tackle its effects. Flavonoids such as resveratrol have been identified as potent inhibitors of the induction of CYP1 both *ex vivo* and *in vivo* by acting as competitive antagonists for the aryl hydrocarbon receptor AhR, involved in the activation of CYP1 expression[23]. This is possibly due to structural similarities with typical AhR ligands[24], which means compounds with different structural features can have more potent inhibitory effects in different isoforms of the enzyme. For example, myricetin and quercetin are potent CYP1B1 inhibitors but appeared to be less effective on the CYP1A1 and CYP1A2 isoforms[25].

Furthermore, other authors have reported the role of some flavonoids as AhR agonists and CYP1 substrates[24]. In this case, the expression of CYP1 isoforms is facilitated via AhR-mediated induction of the *Cyp1* gene, but structural similarities of flavonoids to steroid hormones make flavonoids likely substrates[25], diminishing the harmful activity of CYP1 enzymes when they are targeted in lieu of PAHs and other pro-carcinogens. Additionally, enzymatic modification of flavonoids often gives rise to structures with improved anti-carcinogenic properties upon delivery at CYP1-expressing tumour sites[25].

Overall, flavonoids can exert different effects on the CYP1 family, acting either as AhR-antagonists/inhibitors, as AhR-agonists/substrates or having a combined inhibitor/substrate effect. The latter is the case with resveratrol, which can also be transformed into molecules with improved anti-carcinogenesis properties[24].

### *Flavonoids as ABC transporters regulators*

The ABC (ATP-binding cassette) superfamily is an evolutionarily-conserved family of transporters that comprises P-glycoprotein (P-gp), breast cancer resistance protein (BCRP, also known as ABCG2) and multidrug resistance proteins 1 and 2 (MRP1 and 2). These membrane proteins are involved in the absorption, disposition and secretion of xenobiotic compounds. They are the main family of drug efflux transporters and are involved in the disposition of clinically-used drugs[26]. Particularly, BCRP has been detected in a number of

human tumours, including breast cancer, and represents a prominent mechanism for the development of multidrug resistance (MDR). Its overexpression in tumour sites leads to active exclusion of cytotoxic agents, limiting their absorption and intracellular accumulation and therefore hindering the effect of some cancer treatments[27].

There is accumulating evidence for the existence of flavonoid-drug interaction with BCRP. In the last decade extensive screenings have proved the effect of flavonoids as inhibitors of BCRP[26,28], showing that their intake during cancer treatment can cause an increase in the bioavailability and accumulation of antineoplastic agents[29], thus reversing MDR.

Flavonoids induce these effects by acting as inhibitors of the transporters, limiting the ATP-hydrolysing action that leads to exclusion of anticancer drugs from tumour tissues [30]. This probably takes place by binding to nucleotide binding domain (NBD), which is targeted by flavonoids both in BCRP and P-gp[31]. Despite the positive alteration of drug pharmacokinetics induced by flavonoids, their interaction with BCRP is yet to be completely understood. For instance, some flavonoids can act as BCRP substrates (competing for the transporter with other substrates[26]), whereas other compounds can even induce expression of ABC transporters, stimulating BCRP-mediated MDR[32].

#### *Effect of flavonoids on apoptosis, cell cycle arrest and other signalling pathways*

Numerous flavonoids have been shown to induce apoptosis in a wide range of cancers (including breast[33]) through both main apoptotic pathways: intrinsic, caspase-9 and mitochondrial-driven apoptosis; and extrinsic, caspase-8 and death receptor-driven apoptosis[34].

They can also modulate other important regulators of apoptosis, including PARP (poly ADP-ribose polymerase)[35], anti-apoptotic protein families FLIP (FADD-like inhibitory protein) and Bcl-2 (B-cell lymphoma 2)[33,36] or regulatory genes such as *p53*[37]. Flavonoids such as quercetin can also inhibit proteins involved in the evasion of apoptosis, such as sphingosine kinase[37] and protein kinase B (AKT)[38].

Ultimately, these discoveries highlight the broad and complex effect of flavonoids as pro-apoptotic drugs. In fact, some flavonoids have also been observed to play a counterintuitive role as competitive inhibitors for some caspases, suggesting that alternative, non-caspase dependent apoptosis pathways may be involved in their actions[39].

Cell cycle arrest has also been identified as one of the main mechanisms behind the anti-tumour effect of flavonoids. Both naturally-occurring and novel flavonoids have been shown to arrest proliferation at the G2/M checkpoint in several different cancer types[7,37], mainly through modulation of the expression level of different cyclins[35].

Through different mechanisms, linked to their properties as antioxidants, oestrogen-agonists or CYP1-inhibitors, flavonoids can also modulate proliferation, invasion or inflammatory signals. For instance, resveratrol inhibits cyclooxygenases 1 and 2 (COX1 and COX2)[40], involved in the production of prostaglandins that subsequently leads to cell proliferation,

angiogenesis and immunosuppression[2]. Different flavonoids have also been reported to modulate inflammatory signalling by mechanisms such as down-regulation or inhibition of the nuclear factor-kappa B (NF- $\kappa$ B)[41], therefore inhibiting proliferation and survival.

A recent meta-analysis has shown the relationship between flavonoid consumption and the reduction of chronic systemic inflammation mediators[42], while other reviews have shown evidence supporting the ability of flavonoids to inhibit metastasis, invasion and progression of cancer[43].

#### *Promise of flavonoids as pharmacological agents against breast cancer*

A major factor in the potential of flavonoids as anticancer agents lies in the complex manner in which they exert different effects. Firstly, research has described the anti-tumour effects of flavonoids as being not only dose-dependent, but also biphasic[36]: whereas lower concentrations that could easily derive from a regular dietary intake have anti-apoptotic or cytoprotective effects, higher concentrations (by a factor of between 5 and 10) can cause a pro-apoptotic response involving phenomena such as DNA-damage[44]. Indeed, low concentrations of flavonoids such as genistein, resveratrol or myricetin may act as oestrogen agonists and cause proliferation of breast tumour tissues in an ER-dependent manner, whereas higher concentrations in the micromolar range exert AI and cytotoxic effects[10,12]. Nevertheless, the concentrations required to exert the desirable effects of flavonoids are still feasible from a pharmacological point of view, as opposed to other models in which anti-mutagens and anti-carcinogens are administered at unrealistically high doses, which would probably hinder the translation of these therapeutic strategies to the clinical setting[45]. Additionally, a major setting for the application of flavonoids is as sensitisers or co-treatments to achieve synergistic effects in combination with other therapies, which means the concentrations required in treatment would potentially be lower and their administration and delivery easily achievable.

Furthermore, the anti-cancer effect of flavonoids has been proved to be broad (affecting most types of cancers) but cancer-specific, since normal cells remain unaffected by concentrations that induce pro-apoptotic effects on cancer cells[36]. This is probably due to the fact that flavonoids target pathways typically characteristic of cancer cells. For instance, CYP1 has been shown to be selectively expressed in tumour cells and pre-malignant tissue, not being significantly present in normal surrounding tissues[25]. This shows a great potential for the development of therapies targeted specifically to the abnormal tissue, and this specificity could also be enhanced because the compounds used are often only bioactivated when exposed to the effect of these enzymes.

Flavonoids also work in an additive manner. Hence, the combination of different polyphenols administered concomitantly with anticancer treatments has been suggested as one of the promising strategies for the application of flavonoids to cancer treatment[46]. Interestingly, research has also shown that flavonoids do not hinder other anticancer natural processes (such as the effect of phase II detoxifying enzymes[47]).

## Conclusions

Research in the last few decades has provided extensive evidence of the great versatility of flavonoids and the numerous targets that make them a compound family with great potential as anticancer agents. These properties seem to be largely linked to their relatively simple structure: the presence of conjugated electron systems and aromatic rings make them stable and reactive, whereas their overall structure allows them to act as substrates, inhibitors or agonists for numerous enzymes or molecules involved in the development and progression of cancer.

To summarise, the combination of said multiple targets of flavonoids and the positive pharmacological characteristics of the effects they exert add up to the potential of these compounds in cancer treatment. Such versatile biological activity implies a great underlying complexity in the true mechanisms of action of different flavonoids, often dependent on a fine balance between pro- and anti-oxidant properties or between other beneficial and detrimental effects (see *Figure 1*). Further study is needed for a better understanding of this, also taking into consideration the consequences of long term exposure to compounds as ubiquitous as these or the variable effects due to specific structure-activity relationships[29–31].

Despite this complexity, meta-analyses of controlled intervention trials and studies *in vivo* have shown that the application of flavonoids in the right setting and conditions can ultimately lead to a very positive outcome: decreasing indicators of inflammation, limiting proliferation, increasing latency and reducing both tumour size and metastasis[42]. The accumulating knowledge on the mechanism of action of flavonoids, as briefly summarised here, together with information on different structure-activity relationships has led to promising new research rationales. In fact, there are several examples of promising novel flavonoids with improved properties that are currently at different stages of development towards their potential application in the treatment of ovarian and breast cancer[48–50].

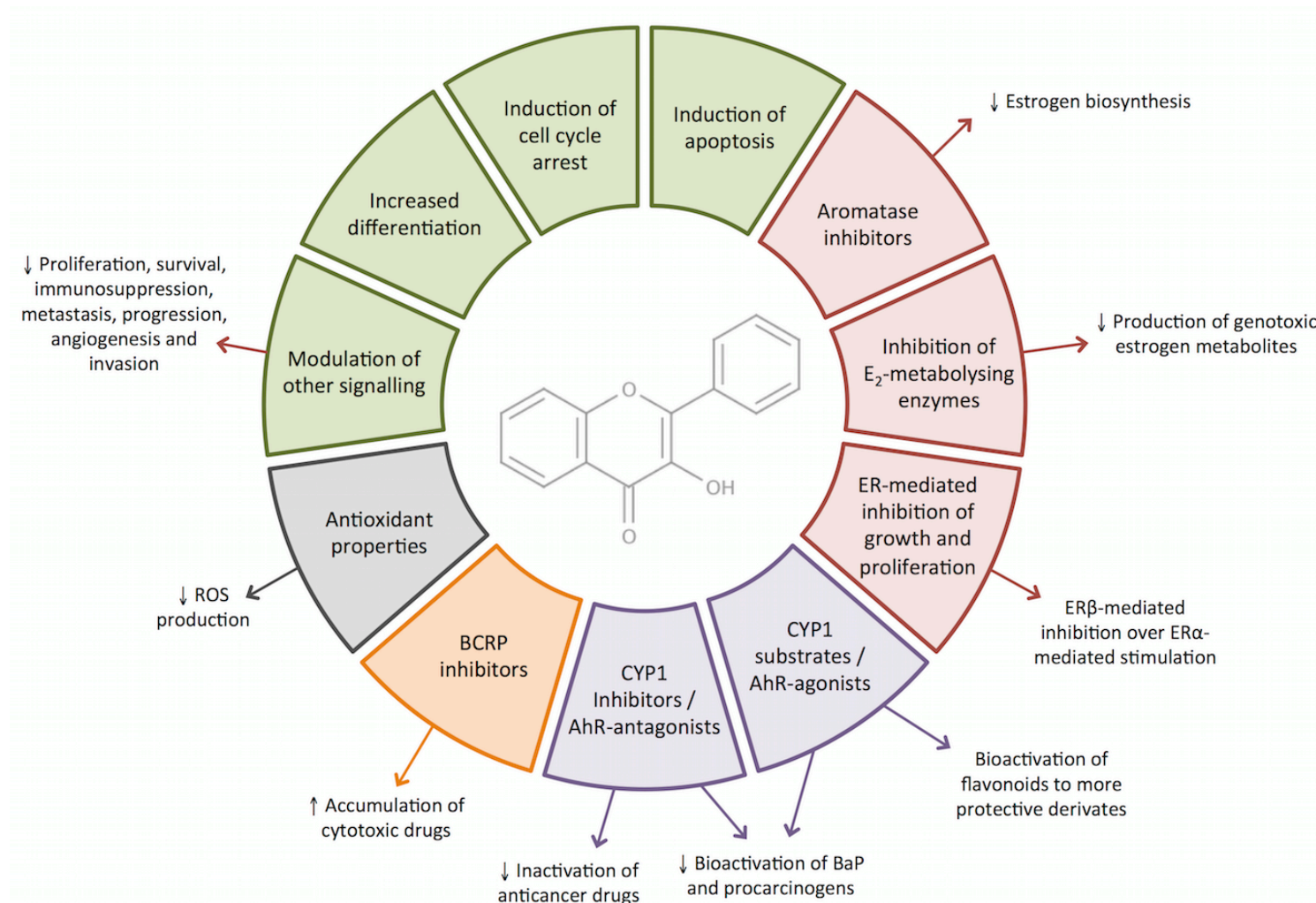
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**Figure 1** A broad range of beneficial antitumour properties have been reported for flavonoids. Their effect on oestrogen production and signalling pathways has been linked to their role as aromatase inhibitors and their interaction with ER and oestrogen-metabolising enzymes. They act as BCRP inhibitors and interact with the CYP1 both as inhibitors and substrates. Research has also shown their ability to induce apoptosis and cell cycle arrest and to alter numerous signalling pathways involved in cancer-related phenomena such as inflammation and proliferation.

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